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# Autosomal Dominant Inheritance of Hypothalamic Hamartoma Associated With Polysyndactyly: Heterogeneity or Variable Expressivity?

**Theresa A. Grebe and Carol Clericuzio**

*Department of Pediatrics, Division of Medical and Molecular Genetics, University of Arizona College of Medicine, Phoenix (T.A.G.); and Department of Pediatrics, Division of Dysmorphology / Clinical Genetics, University of New Mexico School of Medicine, Albuquerque (C.C.)*

**We report on a two-generation family exhibiting dominant inheritance of complex polysyndactyly associated with hypothalamic hamartoma. These individuals have some manifestations of Pallister-Hall syndrome (PHS), but their phenotype is milder. The proposita is a 16-year-old girl with polysyndactyly of the hands and feet, short stature, and a large hypothalamic hamartoma. Her brother and father also have polysyndactyly and a hypothalamic mass on MRI scan. All three have normal appearance and intelligence, with normal pituitary function. Several other paternal relatives have polysyndactyly as well. We propose that this family may represent a clinically and perhaps genetically distinct entity from PHS, based on normal survival, normal intelligence, lack of endocrine dysfunction or facial anomalies, and few other structural malformations. Linkage analysis is in progress to determine whether this represents a benign form of PHS or a genetically separate condition. The phenotypic differences between these cases and classic PHS have important prognostic and recurrence risk implications.** © 1996 Wiley-Liss, Inc.

**KEY WORDS: hypothalamic hamartoma, polysyndactyly, dominant inheritance, Pallister-Hall syndrome, Y-shaped metacarpal, magnetic resonance imaging**

## INTRODUCTION

We report on a family with autosomal dominant inheritance of hypothalamic hamartoma associated with complex polysyndactyly of the hands and feet. The clinical findings in this family are similar to, but more benign than those of Pallister-Hall syndrome (PHS). We propose that this family represents either a mild expression of PHS, or a distinct genetic syndrome showing phenotypic overlap with PHS.

## CLINICAL REPORTS

The proposita is a 16-year-old girl who initially presented with complex polysyndactyly of the hands and feet and proportionate short stature. She was the product of an uncomplicated term gestation to a 27-year-old gravida 4 para 3 mother and a 28-year-old unrelated father. The maternal weight gain was 40 lbs. and the fetal activity was normal. She was born by vertex vaginal delivery with no complications. Her birth weight was 3,400 g (50–75th centile) and birth length was 56 cm (>95th centile). Complex polysyndactyly involving the hands and feet was noted at birth. Her postnatal growth was at the 2nd centile for height, 25th centile for weight and 25th centile for head circumference. There were no known abnormalities of the epiglottis, anus, or of lung lobation. By history she had a short lingual frenulum with an associated speech impediment. A gap between her upper central incisors had been corrected by dental appliances.

On physical examination at age 14 years, her height was 148 cm (<5th centile), weight 47 kg (25th to 50th centile), and head circumference 53 cm (2nd to 50th centile). Her cranium demonstrated a craniotomy scar. She was normal in appearance (Fig. 1a). She had Tanner IV breast and pubic hair development. Her hands were status postpolysyndactyly repair. She had six digits with partial duplication of the third metacarpal associated with a complete extra digit (Fig. 1b). There was a wide space between digits 3 and 4 and a single knuckle

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Address reprint requests to Theresa A. Grebe, M.D., University of Arizona, Phoenix Genetics Program, Maricopa Medical Center, P.O. Box 5099, Phoenix, AZ 85010.

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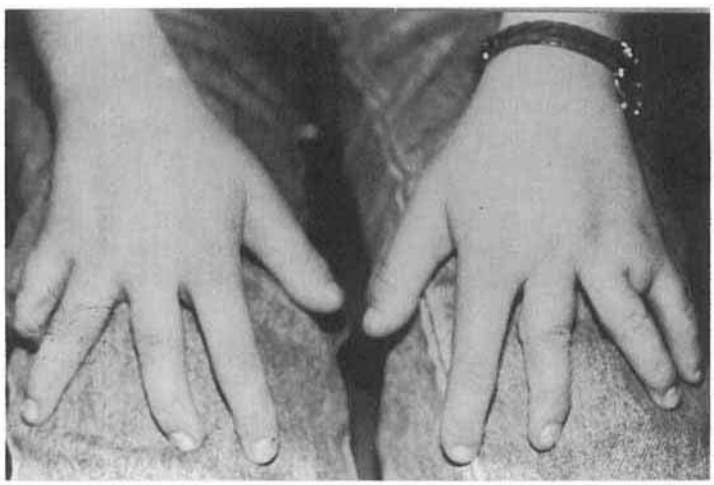

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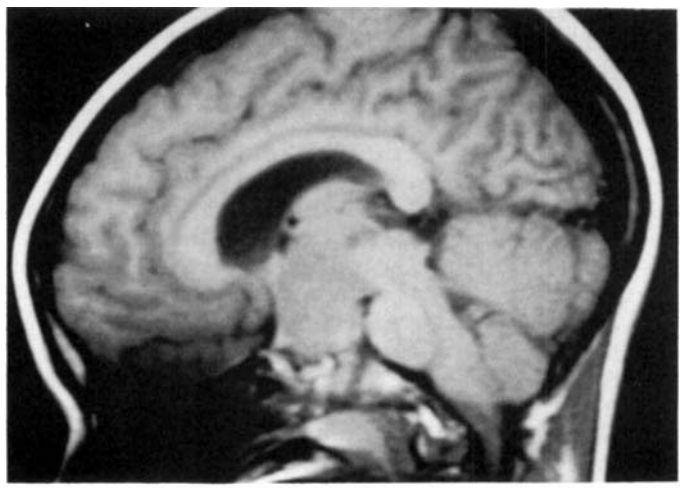

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Fig. 1. **a**: Frontal view of proband showing normal appearance. **b**: Hands of proband. Note central polydactyly, wide space, and single knuckle between digits three and four. **c**: Hand X-rays of proband. Note the Y-shaped third metacarpals. **d**: Sagittal T1-weighted image of proposita demonstrating a 3-cm mass extending inferiorly from the region of the hypothalamus into the suprasellar, prepontine, and interpeduncular cisterns. **e**: The mass remains isodense with gray matter on axial T2-weighted images. The cerebral peduncles are splayed laterally around the mass, and the temporal horns are slightly prominent.

between these two digits. She had 7 digits on the right hand with syndactyly of digits 5,6, and 7. Preoperative X-rays showed Y-shaped, partially bifid third metacarpals, associated with duplication of the third rays (Fig. 1c). The fourth metacarpals were hypoplastic, especially proximally. The left fourth digit was hypoplastic and the right was absent. The distal fifth digits were also hypoplastic, and the right fifth was broad and irregularly shaped, suggesting partial duplication as well. She also had a supernumerary toe on the right foot with syndactyly of the 4th and 5th toes.

Evaluation for short stature demonstrated hypertension and borderline renal function with blood urea nitrogen 25 mg/dl (normal = 7–18), creatinine 1.4 mg/dl (normal = 0.6–1.3), creatinine clearance 31 ml/min (normal = 72–141), and 24-hour urine protein 152 mg/l (normal = 0–135). An intravenous pyelogram demonstrated chronic vesicoureteral reflux on the right with severe atrophy and blunting of the calyceal system. The upper pole of the left kidney was absent, but the mid- and lower poles had normal parenchymal thickness. Endocrine evaluation was normal. Laboratory studies showed the

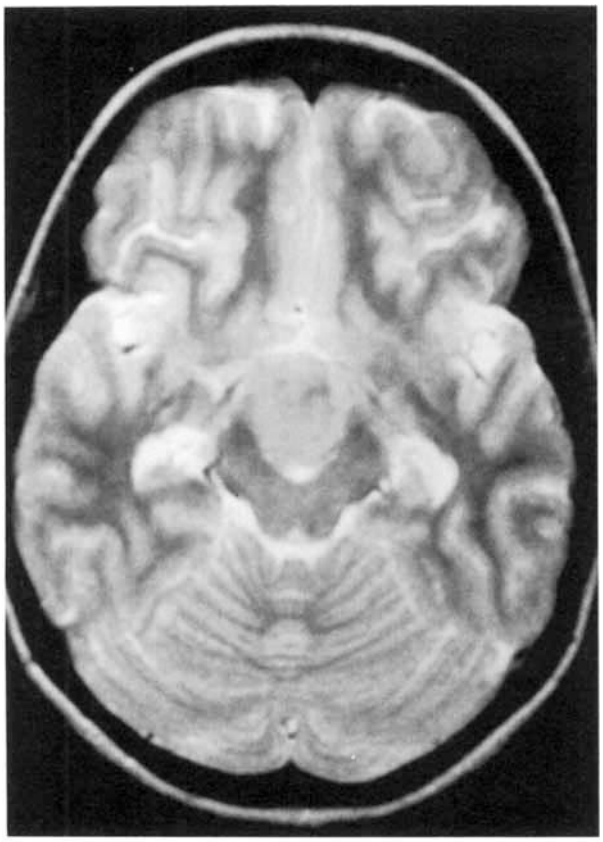

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Fig. 1. (*Continued.*)

following: T4 8.4 μg/dl, T3UP 37%, T7 3.1, thyroid stimulating hormone 2.0, AM cortisol 15 μg/dl (normal = 6–21), follicle-stimulating hormone 1.5 mIU/ml (normal < 15), luteinizing hormone 11 mIU/ml (normal = 3.8–15), prolactin 12.4 ng/ml (normal = 3.2–20), human growth hormone <0.6 ng/ml (normal < 20), AM ACTH 14 pg/ml (normal = 9–52). A high-resolution chromosome study demonstrated a 46, XX karyotype.

Cranial magnetic resonance imaging (MRI) was performed because of a history of chronic headaches, and showed a 3.0-cm mass extending inferiorly from the region of the hypothalamus into the suprasellar, prepontine and interpeduncular cisterns (Fig. 1d,e). The cerebral peduncles were splayed laterally around the mass, and the temporal horns of the lateral ventricles were slightly prominent. This was partially resected and multiple biopsies were sent for histologic examination. Microscopic evaluation demonstrated areas of normal neural parenchyma resembling cortex and white matter. Within this tissue were aggregates of very large, atypical neurons intimately surrounded by a delicate capillary network. These findings indicated a diagnosis of hypothalamic hamartoma. Following surgery, the patient suffered from short-term memory loss and continued headaches, although prior to this she was neurologically intact.

Family history (Fig. 2) is significant for multiple affected relatives, some with isolated polysyndactyly, and some with both polysyndactyly and central nervous system (CNS) involvement. An older brother (IV-2) has polysyndactyly of the hands and feet, and has a normal MRI scan of the brain. A younger brother, (IV-7), was also born with polysyndactyly of both hands and the right foot. He was the 7-year-old product of an uncomplicated term gestation, born to a 36-year-old gravida 7 para 5 spontaneous abortion 1 mother. His birth weight was 3.6 kg (50th to 75th centiles) and birth length 51 cm (50th to 75th centiles). He has had normal growth and development, and is currently in a regular elementary class. A gap is present between his upper central incisors, and he has a short lingual frenulum with a speech impediment. He had a left hydrocele with

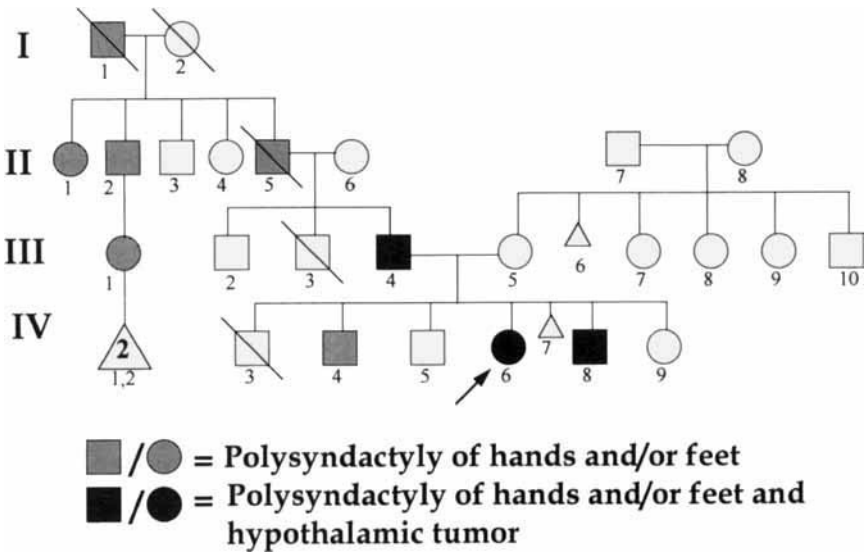
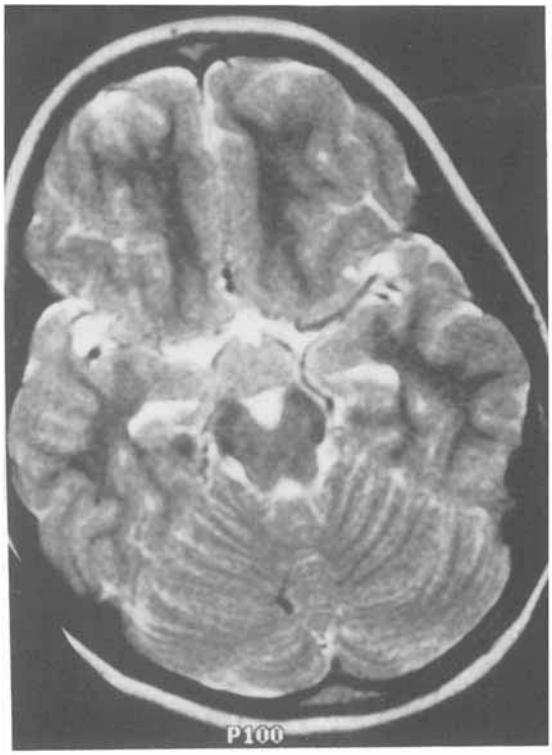



Fig. 2. Pedigree of family with hypothalamic hamartoma and polysyndactyly.

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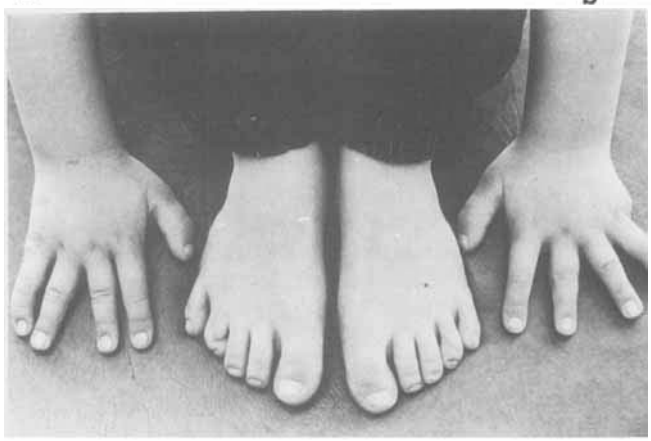

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Fig. 3. **a**: Axial T2-weighted image of cranial MRI scan of proposita's brother (IV-7). Note a similar suprasellar mass at the base of the hypothalamus. **b**: Frontal view of proposita's brother (IV-7) showing normal appearance. **c**: Hands and feet of IV-7. Note the repaired polysyndactyly and wide space between digits three and four. **d**: Preoperative hand X-rays of IV-7. Note the Y-shaped metarcarpals. **e**: Right foot X-ray of IV-7. There is partial duplication of the third ray.

inguinal hernia, and unilateral choanal atresia which were surgically repaired. An MRI scan of the brain, done because of headaches at age 7, showed a similar, though smaller suprasellar mass as compared with the sib, and this was presumed to be a hypothalamic hamartoma as well (Fig. 3a). Endocrinologic evaluation demonstrated normal pituitary function with normal hypothalamic and adrenal reserve. He has no known abnormalities of the epiglottis, anus, kidneys, or lungs.

On physical examination, height was 126 cm (80th centile), weight 26.5 kg (85th centile), and head circumference 54.5 cm (98th centile). The face was normal, with a right nasal stent in place (Fig. 3b). His hands showed repaired postaxial polysyndactyly, with a nearly complete extra digit on one hand which

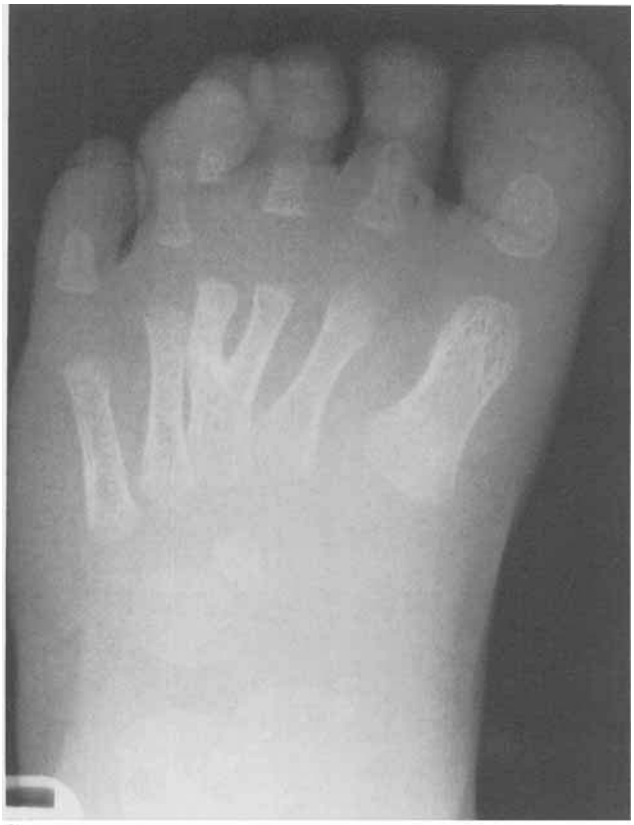

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Fig. 3. (*Continued.*)

had been surgically removed, and a tiny soft tissue protuberance on the other hand. As in the proposita, there was again a wide space and single knuckle over digits 3 and 4 (Fig. 3c). Preoperative X-rays showed partial duplication of the third metacarpals bilaterally (Fig. 3d). The right foot had partial duplication of the third ray, with a hypoplastic digit between 3 and 4, and partial duplication of the third metatarsal (Fig. 3e).

The father, (III-6) is a 43-year-old healthy man with polysyndactyly of the hands, and a gap between his upper central incisors. His past medical history was unremarkable until the recent onset of headaches, and he has had no problems with infertility. A formal endocrine evaluation has not yet been performed. He also had no known abnormalities of the epiglottis, lungs, kidneys, or anus. On physical exam, he was 175 cm tall and had a normal phenotype (Fig. 4a). His hand findings are similar to his children's with a wide space between digits 3 and 4, with a single knuckle in that area (Fig. 4b). His cranial MRI scan showed a 1.5-cm mass in the suprasellar cistern, extending into the interpeduncular cistern. The pituitary gland appeared normal (Fig. 4c).

The family history is otherwise positive for polysyndactyly of the hands in the paternal grandfather (II-5), polydactyly of the feet in the paternal great-aunt (II-3), polydactyly of the hands in the paternal great-uncle (II-1), second-cousin (III-1), and great-grandfather (I-1). All of these individuals are reported to have a gap between their upper central incisors. None of the other individuals were reported to have had polydactyly, nor have they had MRI scans. The mother in this family had one miscarriage (IV-7) at 16 weeks gestation. The cause of death was not determined, but no polydactyly was noted. One interesting additional note on the family history is that the father is a descendent of the original family reported with autosomal dominant proximal symphalangism by Harvey Cushing in 1916. This family was traced through seven generations and was found to be descended from William Brown, a Scottish immigrant to Virginia in the 1740s. The family was first brought to Cushing's attention by a woman who presented to him with a "cerebral glioma" and symphalangism. Although the hand findings are clearly different than those of our patients, a link between these two conditions seems quite probable.

## DISCUSSION

The clinical findings in these patients overlap but are clearly more benign than those of PHS. Hall et al. [1980] initially reported this lethal malformation syndrome in six infants with a hypothalamic hamartoblastoma, postaxial polydactyly, and imperforate anus. They also exhibited many other findings, including intrauterine growth retardation, facial anomalies, pulmonary malformations, clefting, distal limb shortening, and cardiac malformations. All died in the neonatal period, presumably due to hypopituitarism and adrenal insufficiency.

A comparison of the clinical manifestations seen in these patients to those of PHS shows several important differences (Table I). The histologic findings of the hypothalamic tumors in these patients differ in a number of aspects. Clarren et al. [1980], in an accompanying article to Hall et al. [1980], calls these tumors hypothalamic hamartoblastomas, defined in Stedman's Medical Dictionary [1982] as "a malignant neoplasm of undifferentiated anaplastic cells thought to be derived from a hamartoma." This term is used to emphasize both the malformational and neoplastic properties of the tumors. The cells are typified by small nuclei, and resemble undifferentiated germinal brain cells. "While no mitotic figures or pleomorphic elements are found, the neoplastic nature of the tumors is suggested by the size of the mass and its invasion and destruction of more peripheral hypothalamic nuclei" [Clarren et al., 1980, p.81].

The tumor found in our patient, however, is described as a hamartoma, which is defined as "a focal malformation . . . composed of an abnormal mixture of tissue elements, or an abnormal proportion of a single element, normally present in that site which develops and grows at virtually the same rate as normal elements. . . ." [Stedman's Medical Dictionary, 1982]. This type of tu-

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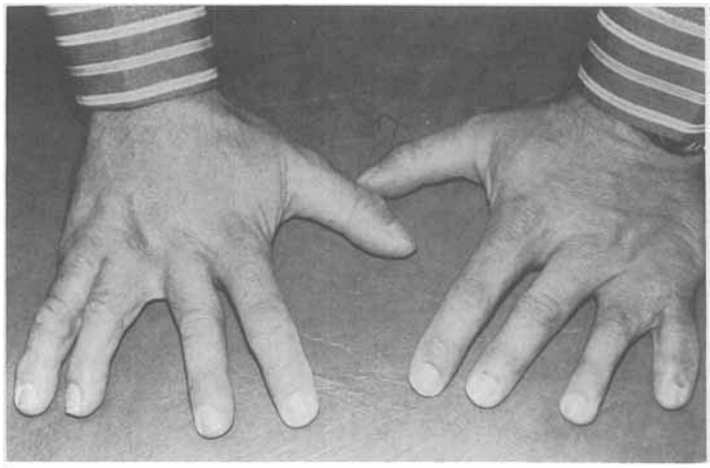

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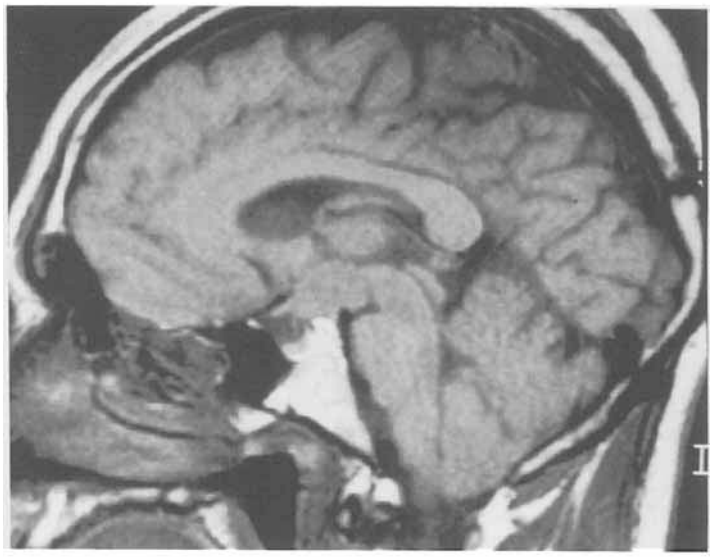

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Fig. 4. **a**: Frontal view of proposita's father (III-6). **b**: Hands of III-6. Note wide space and single knuckle between digits three and four. **c**: Sagittal T1-weighted image of cranial MRI scan of III-6. Note the 1.5-cm hypothalamic mass. The pituitary gland has a normal appearance.

mor is benign, and is composed of mature neuronal tissue. Although it may exert pressure on surrounding structures as it grows, it is not locally invasive. Graham et al. [1986] reported a patient with PHS and such a tumor with long-term survival. Surgical specimens from this patient at 1 year of age showed mature gray matter, also consistent with a hypothalamic hamartoma. The authors hypothesized that, based on these histopathologic findings, hypothalamic hamartoblastomas retain the potential to develop into more mature neural elements over time. Such tissue maturation has been documented in neuroblastomas, another primitive germ cell tumor, adding weight to this theory. The tumors in our patients may also have been examples of this process, although the changes are now impossible to prove.

In the original patients described by Hall et al. [1980], as well as in subsequent cases, the pituitary gland was absent, causing panhypopituitarism and adrenal insufficiency which in most cases led to death in the neonatal period. The present patients were not recognized until much later in life, and have no evidence of pituitary dysfunction. The proposita and her brother had formal endocrine evaluations which were normal, and the father has no history of growth or other hormonal problems. Survival in these cases has been normal to date.

Complex polysyndactyly is present in these patients, as well as in PHS, although the involvement is somewhat different. In PHS the typical changes are noted around the fourth digit. The fourth metacarpals are short and dysplastic with a hypoplastic digit. This was

TABLE I. Comparison of Clinical Findings

| | Described family | PHS |
|---|---|---|
| Hypothalamic tumor | Mature | Primitive |
| Pituitary function | Normal | Abnormal |
| Survival | Normal | Neonatal death |
| Polysyndactyly | Present | Present |
| Imperforate anus | Absent | Present |
| Facial appearance | Normal | Abnormal |
| Other malformations | Few | Many |
| Inheritance | Autosomal dominant | ? |

noted in the proposita only, however, and the most striking abnormality in the present patients is partial duplication of the third metacarpal associated with two complete fingers. This was noted in patient 4 of Hall et al. [1980]. The fifth metacarpal is either partially duplicated, rudimentary or absent in our patients but is normal in the PHS cases. In the feet, the third metatarsal rather than the fourth, is partially duplicated, with an extra complete toe.

Imperforate anus was noted in 5 of 6 of the original patients with PHS, but is not present in any of our patients. The PHS patients are reported to exhibit a short midface, anteverted nostrils, abnormal ears, micrognathia, bathrocephaly, and large fontanels. Our patients have normal phenotypes. Other major malformations are also frequently seen in PHS, including oral frenulae, pulmonary and laryngeal malformations, cardiac, genital, and renal anomalies, and a variety of skeletal malformations. Two of our patients each have a single anomaly (renal anomaly and choanal atresia); they do not exhibit the clinical picture of multiple anomalies seen in the PHS patients.

The inheritance pattern in our cases is clearly autosomal dominant, while that in PHS is much less clear. The initial patients described were all sporadic, and a teratogen exposure was postulated as the underlying cause. There have been several recent reports of recurrences of PHS, suggesting the possibility of autosomal recessive inheritance, or germline mosaicism for an autosomal dominant condition.

Graham et al. [1985] described a term female with typical findings of PHS, who died at 21 hr. The maternal aunt had died at 17 hr with an unusual facial appearance, and polydactyly. No autopsy was performed. Therefore, the diagnosis of PHS could not be documented on the aunt. Kuller et al. [1992] reported on a term male with a hypothalamic hamartoma, microphthalmia, colobomas, cleft lip/palate, normal hands/feet, and a patent anus, who died at 5 weeks. The karyotype was 46,XY,−7,+der(7),t(3;7)(p25.3;q36)pat. A brother died at 3 years with similar manifestations and normal chromosomes. These patients were the first with PHS and a chromosomal abnormality, suggesting a possible gene locus on either distal 3q or 7q. Sills et al. [1993] reported a term male with postaxial polydactyly, microphthalmia, panhypopituitarism, and a hypothalamic mass, alive at 4 years. A female sib with polydactyly, hydrocephalus, and an absent pituitary was aborted at 18 weeks. The same authors [Sills et al., 1994] later reported that this same couple terminated a third pregnancy at 15 weeks, because of ultrasonographic findings of PHS. The fetus had exhibited holoprosencephaly, an enlarged cisterna magna, polydactyly, a short umbilical cord, and short limbs. Hunter and Gallagher [1994] reported on a 2.5-year-old girl and her 2-month-old brother, both with a hypothalamic hamartoblastoma, midface hypoplasia, hypoplastic epiglottis, syndactyly, and imperforate anus. The parents were reported to be normal. Thomas et al. [1994] identified a term female with polydactyly, a normal anus, hypopituitarism, and hypothalamic hamartoma who died at 12 months. Her 30-week gestation premature brother with similar findings died at 9.5 months. The father had polysyndactyly of hands, but no other abnormalities. He had no evidence of endocrine dysfunction; however, brain MRI was not performed. Topf et al. [1993] reported on a 13-year-old boy with polysyndactyly, hypospadias with chordee, small left testicle, preauricular skin tags, imperforate anus, hypothalamic mass, and normal pituitary function. His father had polydactyly, and a hypothalamic mass, with a patent anus. The authors felt that these two patients clearly had PHS, thus implicating an autosomal dominant gene with variable expressivity as the cause of PHS. It should be noted that the propositus in this paper was born to a woman with type I diabetes, which may at least in part account for his genitourinary anomalies. Penman-Splitt et al. [1994] recently described the first case of maternal transmission of Pallister-Hall syndrome. The mother, age 26, had normal survival, and more mild findings, with no endocrine insufficiency, while the child showed the classic PHS phenotype and died at 18 hours of age. Signs exhibited by the mother included short limbs, polysyndactyly, nail hypoplasia, bifid epiglottis, a renal anomaly, short nose with anteverted nares, flat nasal bridge, and learning disabilities. The infant also exhibited the typical facial findings, along with abnormal ears, limb anomalies, absent epiglottis, lung hypoplasia, secundum atrial septal defect, renal hypoplasia, and marked adrenal hypoplasia. CNS anomalies found on autopsy included absent olfactory tracts, absent pituitary, a large arachnoid cyst, and a hypothalamic hamartoblastoma. These authors also postulated either an autosomal dominant mutation or a segregating chromosomal microdeletion as the most likely genetic mechanism in this family. The families reported by Thomas, Penman-Splitt, and Topf, as well as the one presented here, support the possibility of either autosomal dominant transmission of PHS, with variable expressivity, or the existence of a phenocopy of PHS with milder clinical manifestations, but a distinct genetic locus.

Since the original description of PHS, several points of controversy have arisen regarding its diagnosis. These include the following: are all cases of syndromic hypothalamic hamartomas equivalent to PHS? Is the presence of a hypothalamic hamartoma necessary for the diagnosis of PHS? Is PHS a distinct entity or a developmental field defect? The minimum diagnostic criteria for PHS have not been specifically set forth, although most cases exhibit a hypothalamic hamartoblastoma, polysyndactyly, and imperforate anus. Some authors have stretched the phenotype to include other CNS malformations [Finnigan et al., 1991], while others have labeled cases of the CNS tumor and associated anomalies, but without the other two major findings, as PHS [Kuller et al., 1992]. The phenotypic overlap of PHS with several other congenital malformation syndromes has been noted as well. Stephan et al. [1994] described a boy with hypothalamic hamartoma, supernumerary maxillary incisor, and precocious puberty diagnosed with oral-facial-digital syndrome type VI (Váradi syndrome), and noted the similarity to PHS. Muenke et al. [1991] reported a fetus and Hingorani et al. [1991] reported twin fetuses, all with a combination of clinical findings found in oral-facial-digital syndrome type VI (Váradi syndrome), the hydrolethalus syndrome, and PHS. The similarity of manifestations of PHS with those of type II Smith-Lemli-Opitz syndrome has been noted by several authors as well [Donnai et al., 1987; Finnigan et al., 1991]. Diaz et al. [1991–1992] described a 9-year-old boy with a hypothalamic hamartoma associated with Laurence-Moon-Biedl syndrome. Encha-Razavi et al. [1992] reported on three unrelated fetuses with hypothalamic hamartomas, two of whom also manifested a skeletal dysplasia. They noted that among the anomalies associated with PHS, only the skeletal dysplasia was a constant feature. They proposed that the combination of skeletal dysplasia and orofacial abnormalities defined a familial entity they called congenital hypothalamic hamartoma syndrome. Finally, it has been suggested that PHS does not result from the pleotropic effects of a single gene, but represents a developmental field defect. Hennekam et al. [1986] reported on a newborn girl with a median "cleft" face anomaly, a congenital hypothalamic hamartoma, and a complex congenital heart defect. The authors concluded that the defects in that case were due to a midline developmental field defect. Verloes et al. [1992] reviewed 27 cases of congenital hypothalamic tumors associated with other anomalies. Because of the considerable overlap of manifestations between cases, they proposed a new phenotypic classification system which they called the cerebro-acro-visceral early lethality (CAVE) multiplex syndrome.

The family presented here implicates a single dominant gene as the cause of their mild syndromic hypothalamic hamartoma. Whether this represents variable expression of PHS or a genetically distinct entity must be determined by linkage analysis, which is currently underway. Regardless of the genetic cause in this family, their phenotypic differences with classic PHS have important prognostic and recurrence risk implications. A full clinical evaluation, including brain MRI, of parents of affected children is indicated before accurate genetic counseling can be provided for PHS and related conditions.

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